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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON REPORTING OF SUSPECTED TRANSMISSION OF ANY INFECTIOUS AGENT VIA A MEDICINAL PRODUCT

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1. EXECUTIVE SUMMARY

The pharmaceutical legislation, Regulation (EC) No 726/2004, requires reporting of suspected cases of transmission of any infectious agent outside the EU into the pharmacovigilance systems. This guideline also clarifies how such cases should be considered when occurring within the EU.

The guideline provides information on instances that would be considered to be a suspected transmission of an infectious agent by a medicinal product and how these should be reported through pharmacovigilance and quality defect procedures.

The guideline will be complementary to existing texts on pharmacovigilance and the Compilation of Community Procedures concerning quality defects and serves to strengthen the link between these documents and facilitate understanding of the reporting requirements.

2. INTRODUCTION

Article 24 of Regulation (EC) No 726/2004 and Article 104 of Directive 2001/83/EC as amended, concern the Marketing Authorisation Holder's obligations for reporting of any serious adverse reactions occurring either within the Community or in a third country for a medicinal product authorised in the Community (see Annex: summary of all Articles).

This guideline concerns the elaboration of requirements in respect of the new provisions of the legislation as revised in 2004 requiring that the suspected transmission via a medicinal product of any infectious agent be reported via pharmacovigilance procedures. Article 24(2) of Regulation (EC) No 726/2004 and Article 104(4) of Directive 2001/83/EC as amended, specifically requires reporting of such instances when occurring outside the EU. However, the wording of the revised legislation does not address such occurrences arising within the EU, so that further direction is also required in this respect.

Cases of suspected transmission of an infectious agent may arise either as efficacy or safety related issues (e.g. reporting of infections of unclear cause) through pharmacovigilance or as quality related issues through quality defect reporting and clarification is required on appropriate reporting routes.

The guideline is applicable to all medicinal products authorised in the Community.

The guideline is intended to draw attention to reporting responsibilities for Qualified Persons (pharmacovigilance and quality) with regard to suspected transmission of an infectious agent.

3. SCOPE

The guideline provides information on instances that would be considered to be a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product through pharmacovigilance procedures. The various risks associated with different medicinal products are highlighted, although it is considered that any suspected transmission of an infectious agent by a medicinal product is considered to be a serious adverse reaction (*Note bene*: A reaction, contrary to an event, is characterised by the fact that a causal relationship between the product and the occurrence is suspected).

Whereas legislation clearly states the requirement to report suspected cases of transmission of any infectious agent outside the EU into the pharmacovigilance systems, this guideline also clarifies how such cases should be considered when occurring within the EU.

As explained in the introduction, cases of suspected transmission of an infectious agent may arise as quality-related issues as well as safety or efficacy-related issues, and clarification is provided on how best to report in order to fulfil applicable legislative requirements.

The legal framework for pharmacovigilance of medicinal products for human use in the European Union (EU) is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC on the Community code relating to medicinal products for human use, as last amended by Directive 2004/24/EC and by Directive 2004/27/EC (hereinafter referred to simply as Directive 2001/83/EC). It should be noted that although Chapter 3 of Regulation (EC) No 726/2004 and Title IX of Directive 2001/83/EC contain the majority of pharmacovigilance provisions in the legislation, other measures directly relevant to the conduct of pharmacovigilance are found in other chapters and titles of those legislative texts.

4. LEGAL BASIS

Article 24(2) of Regulation (EC) No 726/2004 and Article 104(4) of Directive 2001/83/EC as amended.

5. GENERAL PRINCIPLES

Pharmacovigilance procedures are defined in Directive 2001/83/EC as amended and in Regulation (EC) No 726/2004. Further guidance is given in Volume 9, including requirements for the expedited reporting of serious adverse reactions.

Existing procedural aspects in relationship to pharmacovigilance should be followed to accommodate the new requirement for reporting of suspected transmission via a medicinal product of any infectious agent.

For certain medicinal products, quality defects resulting in the transmission of an infectious agent may, in first instance, not be clearly signalled as a quality defect, and vice versa, for cases arising as pharmacovigilance issues. Additionally, quality defects arising in third countries may not be communicated to the authorities in the EU and this may pose a risk for the same or similar products authorised within the EU.

It is important to note that the established systems for the reporting of pharmacovigilance issues or of quality defects are applicable and depend on how suspected cases of transmission of an infectious agent are initially identified.

These will now be further strengthened by the new requirement for additional reporting into pharmacovigilance systems of suspected transmission of infectious agents by a medicinal product. Consequently, this will ensure that information on all instances of suspected transmission of infectious agents by a medicinal product will be available through one system, i.e. the pharmacovigilance system. Therefore, regardless of whether the issue is related to quality or safety/efficacy, a complete picture will be held, enabling appropriate action, whereas previously two systems needed to be consulted.

Reporting is required for any suspected transmission of an infectious agent by a medicinal product in a third country which has common processes to the same / similar product authorised in the EU. The product in the third country could be identical to that authorised in the EU or could have common manufacturing sites / processes or starting materials used for production.

The Risk Management Plan (RMP) should also consider issues related to potential transmission of infectious agents, where appropriate. The RMP describes the risk management system for a medicinal product, i.e. the set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the

effectiveness of those interventions. The aim of a risk management system is to ensure that the benefits of the medicinal product exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole, with a focus on risk minimisation. This new proactive approach has been recognised in the revised Pharmaceutical Legislation which now includes a specific reference to risk management (Article 8(3)(ia) of Directive 2001/83/EC as amended).

5.1 Reporting of suspected transmission of an infectious agent

The new legislation specifically mentions suspected infectious agent transmission reporting into pharmacovigilance systems only for third country cases.

The relevant Articles, i.e. Article 24(2) of Regulation (EC) No 726/2004 and Article 104(4) of Directive 2001/83/EC as amended, imply that suspected transmission via a medicinal product of any infectious agent should be considered as a serious adverse reaction.

Therefore, any occurrence within the EU of such cases should be reported in accordance with the general reporting requirements for serious adverse reactions.

This is clarified in the revised Volume 9 of The Rules Governing Medicinal Products in the European Union.

For definition and examples of infectious agents covered by this guideline, see Section 5.4.

5.2 Suspected transmission of any infectious agent via a medicinal product arising as a quality defect

Cases of suspected transmission of an infectious agent may first be noted as a quality defect of an authorised medicinal product, either within or outside the EU.

The established procedures for handling quality defects are not altered by the new provisions of Article 24(2) of Regulation (EC) No 726/2004 and Article 104(4) of Directive 2001/83/EC as amended.

The reporting of defective medicines is described in the Compilation of Community Procedures and Exchange of Information. Holders of an authorisation under Article 40 of Directive 2001/83/EC (i.e. manufacturers and importers of medicinal products) are obliged under Article 13 of Directive 2003/94/EC, Article 13 of Directive 91/412/EC and GMP Guide 8.8 to report to their Competent Authority any defect in a medicinal product handled under their authorisation that could result in a recall or abnormal restriction of supply. It is normally the Qualified Person who has this responsibility.

Member States are obliged, in accordance with Article 117 of Directive 2001/83/EC, to take all appropriate measures to ensure that a medicinal product is withdrawn from the market if it proves to be harmful under normal conditions of use, if its composition is not as declared or if the controls on the finished product or during the manufacturing process or other requirement of the manufacturing authorisation has not been fulfilled.

It is normally the responsibility of the MAH/manufacturer to recall a batch and to notify customers accordingly. It is normally the responsibility of the Competent Authority to notify other authorities of the recall using the Rapid Alert procedure.

The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission. In each case, a professional assessment by the Competent Authority must be made of the seriousness of the defect and its potential for causing harm to the patient.

Although product defects are classified as Class 1, 2 or 3 (see: Compilation of Community Procedures, Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects: http://www.emea.eu.int/Inspections/docs/335103en.pdf), any contamination by an infectious agent should be considered as serious and potentially classified as Class 1 or 2. Transmission of Class 1 and Class 2 rapid alerts should be concurrent with the national action but in all cases should be with 24 hours of the initial national notification. Any suspected case of transmission identified and reported as a quality defect should also be reported to the pharmacovigilance systems, within 15 days.

In the case of a suspected transmission of an infectious agent occurring in a medicinal product in a third country which has common processes to the same / similar product authorised in the EU, the manufacturer must inform the importer in the EU. Since the Qualified Person releasing the batch in the EU will ensure that each batch has been manufactured and checked for compliance with the requirements of the Marketing Authorisation, any suspected transmission of an infectious agent should be reported immediately to the relevant Competent Authority.

5.3 Suspected transmission of any infectious agent via a medicinal product arising as a pharmacovigilance issue

Cases of suspected transmission of an infectious agent which are not clearly due to a quality defect may initially arise as safety or efficacy related issues through the pharmacovigilance system.

When occurring outside the EU, the new provisions of Article 24(2) of Regulation 726/2004 and Article 104(4) of Directive 2001/83/EC as amended, specifically require reporting into the pharmacovigilance system. As discussed above (Section 3), any such case occurring in the EU is considered to be serious and requires expedited reporting.

Where investigation shows that the observed reaction is due to a quality defect, the issue should be reported immediately in accordance with the applicable quality defect reporting procedures.

Regardless of the source of any signal and evaluation as to whether a quality issue is involved, all suspected transmissions of an infectious agent must be reported as a serious event according to pharmacovigilance procedures within 15 days.

This is clarified in the revised Volume 9 of The Rules Governing Medicinal Products in the European Union.

5.4 Transmissible infectious agents

The definition in the relevant Articles (see above) results in the applicability of this guideline to all infectious agents, including pathogenic and non-pathogenic organisms.

Transmission of an infectious agent via a medicinal product could arise from a various of causes, and a number of examples are considered as follows:

Contamination of starting materials, particularly for biological products.

Contamination during processing / manufacture

Inadequate inactivation/attenuation of infectious agents as active substances

Promotion of opportunistic infections due to contamination / bioburden of a medicinal product may be an additional hazard for immunosuppressed patients. It should be noted that promotion of opportunistic infections may be reported as the transmission of an infectious agent, in particular for medicinal products for which promotion of opportunistic infections is an unexpected adverse reaction.

Contamination issues

Examples of the types of contaminating infectious agents, which could be considered are: bacteria, fungi, mycoplasma, protozoa, viruses, agents of Transmissible Spongiform Encephalopathies.

The risk with which contamination of starting materials can occur is dependent on the nature of the materials used and the complexity of the manufacturing processes. It is a requirement that adequate viral reduction / inactivation steps are employed in the manufacture of medicinal products and that these are appropriately validated (3.2.1.2(c) Annex I, Directive 2003/63/EC). Guidelines on this subject should be consulted as appropriate (e.g. CPMP/BWP/268/95: Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses; etc.).

It is well recognised that blood / plasma derived products can be a source of a number of contaminants, including pathogenic viruses and potential TSE agents and therefore, these products could be considered to be of higher risk with regard to transmission of infectious agents. Guidelines on this subject should be consulted as appropriate. (eg. EMEA/CHMPBWP/125/04: Guideline on Epidemiological Data on Blood Transmissible Infections; CPMP/BWP/3794/03: Guideline on the Scientific Data Requirements for Plasma Master File (PMF); etc.)

It is a requirement that medicinal products comply with the current revision of the guideline on Transmissible Spongiform Encephalopathies (EMEA/410/01), where various risks associated with TSE are considered. Other guidelines on this subject should be consulted as appropriate (e.g. EMEA/BWP/5136/03, Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to VCJD risk; etc.).

Additionally, the manufacturing process, e.g. aseptic processing versus terminal heat sterilisation has considerably higher risk with regard to microbial contamination. These concerns are normally addressed by robust validation during process development and followed by GMP – controls and inspections (e.g. see Notice to Applicants, Volume 4 - Medicinal Products for Human and Veterinary Use : Good Manufacturing Practice, ANNEX 1).

Other causes

In certain cases, e.g. in the use of Genetically Modified Organisms, there may be a risk of novel recombination events leading to the production of novel pathogenic organisms within the treated individual. Special care is needed with medicinal products manufactured by advanced technology methods.

The route of administration of the medicinal product will also be important in determining the risk associated with transmission of an infectious agent, with the oral route generally being of lower risk than for injected medicinal products.

Vaccine failure, inadequate inactivation / attenuation of, e.g. live vaccines could result in the patient actually acquiring the infection rather than being immunised against it, such as occurred in the past with polio vaccines.

Medicinal products which act by having a direct or indirect effect on the immune status of the patient could lead to the proliferation of opportunistic infections, e.g. certain contaminating bacterial spores which may affect only immunocompromised individuals, or cases of pathogenic infectivity which is not due to the contamination of the medicinal product, but resulting from immune insufficiency due to the pharmacological action. Therefore, the susceptibility of the patient population to any infectious agent should be considered.

In certain cases the suspected transmission of an infectious agent could be confused with other possible causes, such as infection secondary to antibiotic resistance, medication errors, inappropriate handling of the medicinal product and these should also be considered.

6. SUMMARY

Existing procedural aspects in relationship to pharmacovigilance should be followed to accommodate the requirements for reporting of suspected transmission via a medicinal product of any infectious agent.

The transmission via a medicinal product of any infectious agent is considered to be a serious adverse reaction. Whether occurring within or outside the EU any suspected transmission should be reported within 15 days, in accordance with the requirements for serious adverse reactions, as also explained in Volume 9.

If a report is received of a suspected transmission via a medicinal product of any infectious agent, a risk analysis should be performed by the Marketing Authorisation Holder (MAH), which will also consider, as appropriate: the potential sources of contamination, possibility of reversion to infectivity or promotion of opportunistic infections associated with the product in question. The risk to the patient of these potential sources / promotion of infectivity should be considered and identified.

In conjunction with the risk assessment provided by the MAH, an assessment of the implications for the Marketing Authorisation of the product in question will then be undertaken by the competent authorities.

During the pre-authorisation phase, the applicant should consider the potential for any transmission of infectious agents and discuss this in the risk management plan.

Quality and Safety issues are closely linked and pharmacovigilance reporting is required. Any suspected transmission via a medicinal product of any infectious agent will normally be considered to be due to a quality defect and appropriate action will be taken according to currently defined procedures.

ANNEX I: Summary of Article 24, Regulation (EC) No 726/2004

Article 24(1) requires that suspected serious adverse reactions occurring in the EU and reported by a health care professional for a product authorised centrally within the Community are reported by the Marketing Authorisation Holder (MAH) within 15 days to the Member States within the territory of which the incident occurred.

The MAH should also report suspected serious adverse reactions of which he may reasonably be expected to be aware, in a similar way.

Article 24(2) requires that any suspected serious unexpected adverse reactions (and for veterinary products, human adverse reactions) and suspected transmission via a centrally authorised medicinal product of any infectious agent occurring in the territory of a third country are reported promptly by the MAH to the Member States and the Agency and no later than 15 days following receipt of the information.

Reporting of suspected unexpected adverse reactions which are not serious, whether in the Community or in a third country should follow the procedure referred to in Article 87(2).

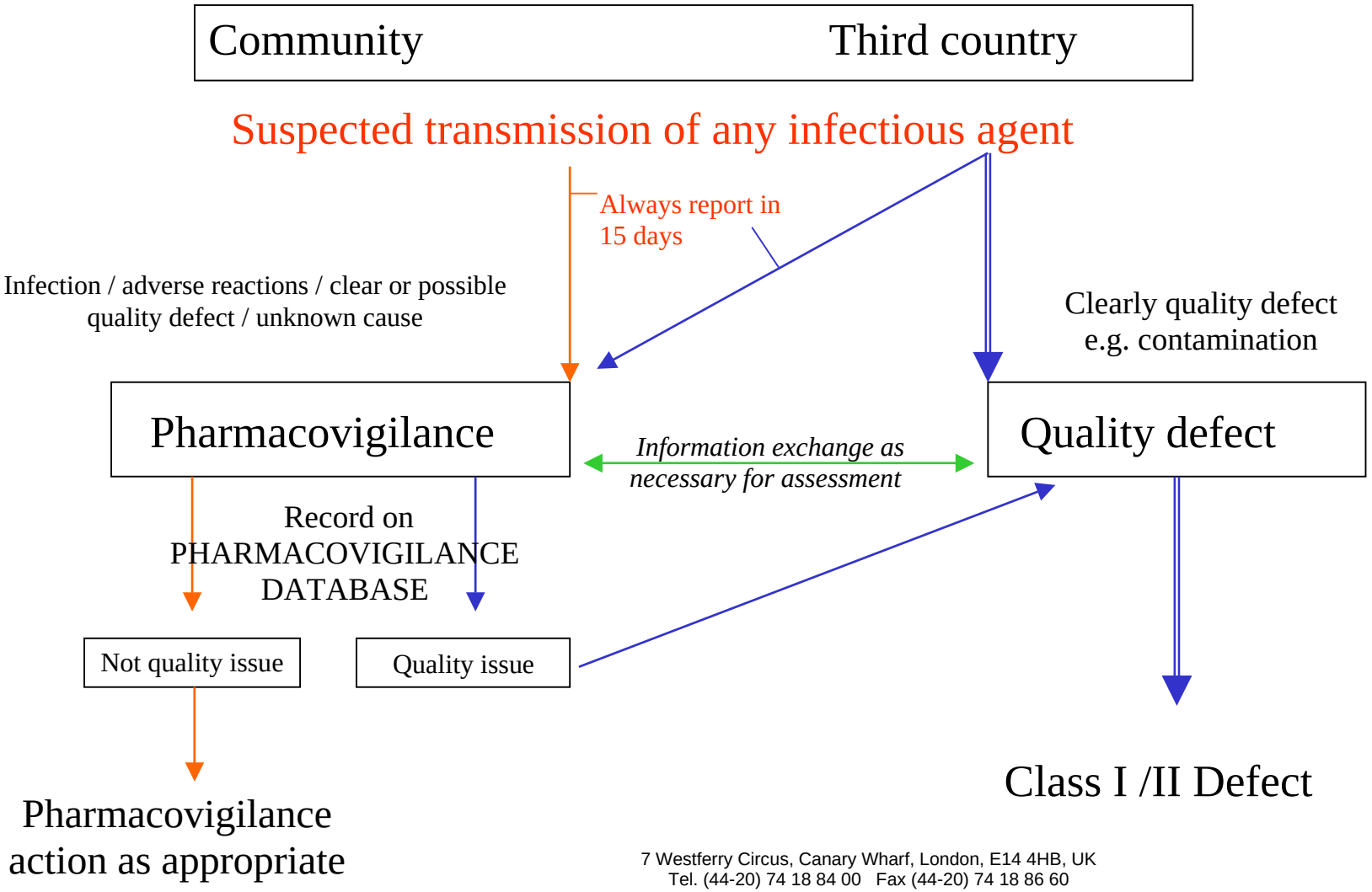
Article 24(3) requires that the MAH shall maintain records for all suspected adverse reactions within or outside the Community which are reported to him, and for human products only, by a health care professional. These suspected adverse reactions shall be reported in the form of a periodic safety update report immediately upon request or according to the periodicity laid down in the aforementioned articles.

Article 24(4) enables the Commission to amend paragraph 3 of Article 24 based on experience gained with its operation.

Article 24(5) states that the Marketing Authorisation Holder may not communicate pharmacovigilance concerns to the public without the prior consultation with the Agency and any information which is not objective or is misleading should be dealt with by appropriate penalty.

Similar provisions are laid down in Directive 2001/83/EC as amended regarding products authorised by other mechanisms than the central procedure.

ANNEX II: Figure describing pharmacovigilance and quality defect reporting.



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